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PIM1 Expression And Regulatory Mechanisms: Decoding Its Significance In Liver Hepatocellular Carcinoma (LIHC) Pathogenesis

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Abstract

The investigation focused on explaining the role of PIM1 expression and its regulatory mechanism in liver hepatocellular carcinoma (LIHC). Using the UALCAN database, PIM1 expression assessment revealed a critical down-regulation in malignant cells as compared with normal controls, suggesting its contribution in LIHC proliferation. Further, taking apart PIM1 expression across various boundaries showed unsurprising down-regulation in different cancer development stages, racial groups, genders and age classes inside LIHC patients, characteristics for its essential role in cancer proliferation. Validation of PIM1 expression done by Utilizing the GEPIA2.0 database, which showed PIM1 was lowly expressed in LIHC cancer as compared to normal control samples. Additionally, dismantling PIM1 validation across different stages of cancer showed dysregulation in all four stage with highest expression in stage III and the lowest expression in stage IV. Subsequently, this study investigated the promoter methylation level of PIM1, elucidating a critical correlation between LIHC samples and normal control samples. Analyzing promoter methylation across v[1]arious clinical parameters uncovered huge variations, with particular methylation patterns seen across cancer stages, race groups, genders and age groups. Survival analysis(OS and RFS) utilizing the KM plotter tool showed an epic association between PIM1 expression levels in LIHC patients, with low PIM1 expression exhibited with higher overall survival (OS) while high PIM1 expression experienced shorter DFS. Further upon validation of results of PIM1 expression level. We divided the LIHC patients into low and high expression groups of PIM1. In LIHC, high PIM1 expression level was associated with good overall survival (OS) while low PIM1 expression level was associated with good DFS in LIHC patients. Additionally,

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mutational analysis utilizing the cBioPortal stage revealed that no critical change found in LIHC samples. Overall, these findings cause to notice the intricate contribution of PIM1 in LIHC pathogenesis, underlining its importance as a prognostic biomarker and supportive therapeutic agent in LIHC management.

Key words: *Liver Hepatocellular Carcinoma, Diagnosis, Treatment.*

1. Introduction:

Cancer is considered the most prevalent clinical cause of death among all diseases [1-5]. Liver cancer is one of the five most common cancers globally, with a high death rate [6, 7]. However, the exact causes of hepatocarcinogenesis remain unclear. Liver hepatocellular carcinoma (LIHC) is one of the most widely recognized cancers worldwide, representing one-fifth of tumor incidence in China [8-10]. Notably, the incidence rate (6.3%) and the death rate (10.5%) of primary liver cancer are higher in males. LIHC is the most common subtype (75-85%) of primary liver cancer [11-14]. The risk factors for LIHC include hepatitis B and C virus infections, aflatoxin, excessive alcohol consumption, and obesity. However, the molecular mechanisms contributing to LIHC progression are still not well understood. A majority of LIHC patients experience recurrence after regional resections. The treatment of LIHC with systematic molecular therapies, regional resections, and liver transplants remains unsatisfactory and limited [15-17]. Long noncoding RNAs (lncRNAs) are functionally defined as RNA transcripts that are over 200 nucleotides long with limited protein-coding potential [18, 19]. LncRNA expression profiles are significant markers for various human tumors [20, 21]. Recently, several lncRNAs have been found to play pivotal roles in regulating tumorigenesis, including LIHC [22]. The prognosis for LIHC patients remains extremely poor, highlighting the need for more research to discover and develop effective biomarkers and targets for LIHC diagnosis and treatment [9].

The exceptionally preserved proto-oncogenic protein PIM1 is an unusual serine/threonine kinase, partly because it is constitutively active. Previous studies identified a group of constitutively activated serine/threonine kinases in the PIM murine leukemia virus family, which includes PIM1 [23, 24]. PIM1, a member of the PIM kinase family, has been implicated in the control of cancer cell proliferation, migration, and apoptosis [14, 24, 25]. These enzymes are increasingly recognized as significant mediators of survival signals in tumors, stress responses, and neural development. Additionally, this kinase family is constitutively expressed in some tumors and functions as true oncogenes. Previous studies have shown that overexpression of PIM1 in various human cancers, such as breast cancer and glioblastoma, is well correlated with malignant growth processes, including cell proliferation, cell cycle arrest, apoptosis, migration, invasion, and drug resistance. However, the role and underlying mechanisms of PIM1 in growth and development in LIHC remain unclear. This study was undertaken to test the hypothesis that PIM1 provides a proliferative advantage and regulates gene expression in LIHC.

2. Materials and methods

2.1 Expression analysis of PIM1 in LIHC

UALCAN (http://ualcan.path.uab.edu) is an interactive web tool for in-depth investigation of cancer omics information, encompassing clinical data for 31 types of malignancies [26]. Using data from The Cancer Genome Atlas (TCGA) project, UALCAN enables users to assess protein-coding gene expression and its impact on patient survival across 33 types of malignancies. We analyzed PIM1 expression in normal and LIHC samples by extracting data

from the TCGA platform. Additionally, we examined PIM1 expression considering different clinical parameters such as patient age, gender, and race using the UALCAN database.

2.2 Validation of PIM1 on additional LIHC data set

GEPIA2 (http://gepia2.cancer-pku.cn/), developed by researchers at Peking University, is a powerful bioinformatics tool for extensive gene expression analysis. Providing access to TCGA and GTEx datasets, it enables researchers to explore the complex gene expression landscape across various tissues and tumors, facilitating innovative discoveries [27]. In this study, GEPIA2 was employed to analyze the association between PIM1 expression and prognosis (overall survival [OS] and relapse-free survival [RFS]) in LIHC cancer.

2.3 Promoter methylation analysis of PIM1

The OncoDB dataset serves as an exhaustive platform housing information on cancer-related genes, mutations, expression, promoter methylation levels, and related functional data [28]. We used UALCAN to analyze the promoter methylation level of PIM1 in LIHC. In our investigation, we utilized both UALCAN and OncoDB databases for promoter methylation analysis of PIM1 across various cancer stages, patient races, genders, and ages.

2.4 Survival analysis of PIM1

The Kaplan-Meier (KM) plotter is a pivotal tool in the domain of survival analysis [29]. This web-based portal leverages extensive clinical data to study the impact of specific genes on patient survival across various types of malignancies. KM Plotter's intuitive interface provides Kaplan-Meier survival curves, illuminating how gene expression correlates with patient outcomes. In this study, the KM plotter tool was used to analyze the effect of PIM1 dysregulation on the overall survival (OS) and relapse-free survival (RFS) of cancer patients.

2.5 Mutational analysis of PIM1

cBioPortal is a crucial database in cancer genomics research [30]. It is an open-access resource for interactive exploration of multifaceted cancer genomics datasets, currently providing access to information from over 5,000 tumor samples across 20 tumor studies. The cBio Cancer Genomics Portal significantly lowers the barriers between complex genomic data and cancer researchers, offering fast, intuitive, and high-quality access to molecular profiles and clinical attributes from large-scale cancer genomics projects. This empowers scientists to translate these rich datasets into biological insights and clinical applications.

3. Results

3.1 Expression analysis of PIM1 in normal control and LIHC samples

Utilizing UALCAN, our initial exploration focused on PIM1 expression across both normal and malignant liver cancer tissues (Figure 1). Our findings revealed significant down-regulation of PIM1 expression in LIHC compared to normal samples. This crucial down-regulation suggests a potential relationship between PIM1 expression and the proliferation of LIHC cells.

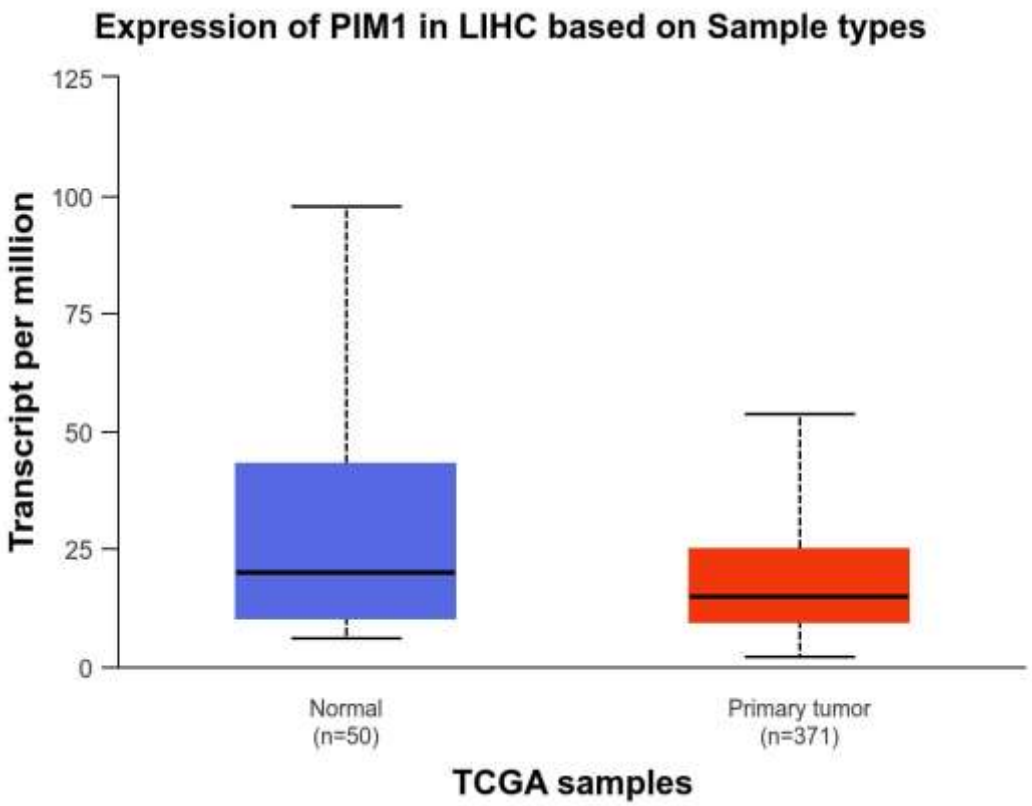


Figure 1: This figure shows the expression profiling of PIM1 in LIHC and normal tissues samples.

3.2 Expression analysis of PIM1 in LIHC samples divided based on different clinical parameters

Concurrently, we conducted an investigation of PIM1 expression in LIHC samples across various clinical parameters, including individual cancer stages, patient's race, gender, and age (Figure 2). Initially, we analyzed PIM1 expression across different cancer stages and observed significant down-regulation of PIM1 in LIHC across all stages compared to normal samples (Figure 2A). Subsequently, we examined PIM1 expression in LIHC patients of different races and found consistent down-regulation of PIM1 in Caucasian and Asian patients, while African-American patients exhibited notable up-regulation of PIM1 compared to normal control samples (Figure 2B). Additionally, we analyzed PIM1 expression in LIHC patients by gender, which demonstrated significant down-regulation of PIM1 in both male and female patients compared to normal samples (Figure 2C). Finally, we investigated the relationship between PIM1 expression and patient age in LIHC, revealing down-regulation of PIM1 expression across different age groups among LIHC patients (Figure 2D).

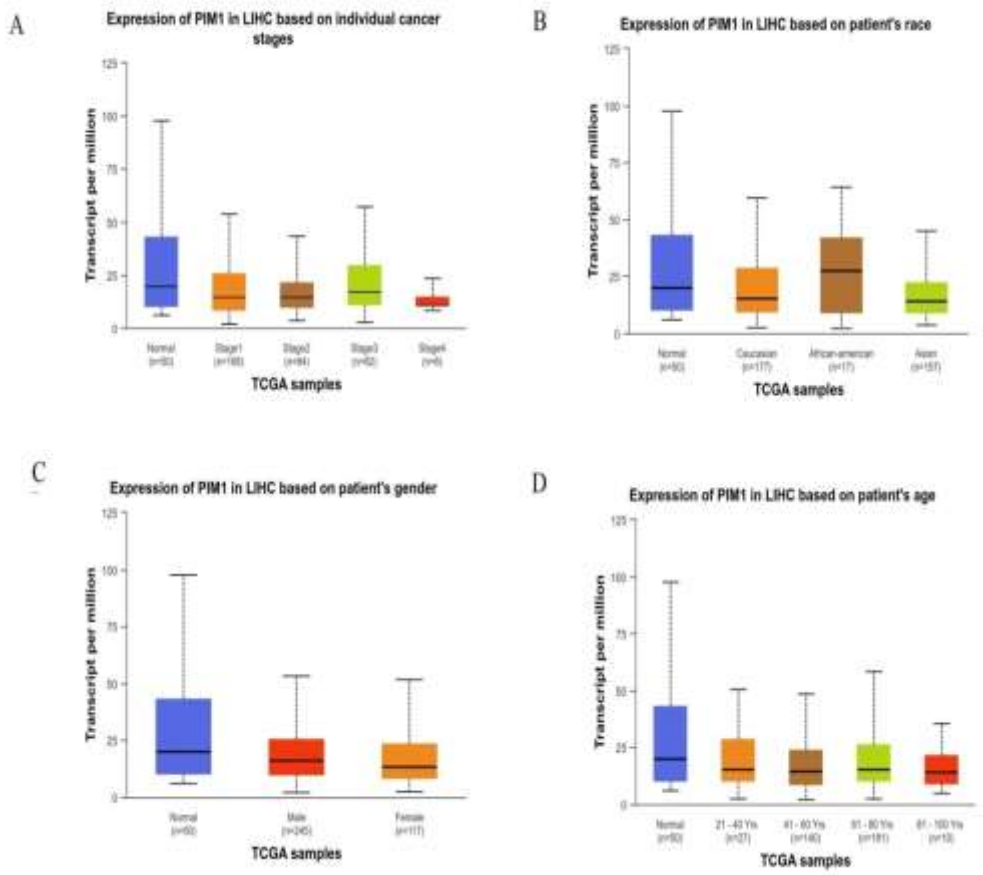


Figure 2: Expression of PIM1 across different clinical parameters.

3.3 Validation of PIM1 on additional LIHC data set

We utilized GEPIA2 to investigate PIM1 expression levels between LIHC tumors and corresponding normal tissues. The results indicated that PIM1 was significantly lower expressed in liver hepatocellular carcinoma (LIHC) compared to normal control samples (Figure 3A). Additionally, we analyzed the correlation between PIM1 expression and pathological stages using the GEPIA2 database. The findings revealed a close correlation between PIM1 expression and the stages of LIHC patients. Specifically, PIM1 expression was highest in stage III and lowest in stage IV of LIHC (Figure 3B).

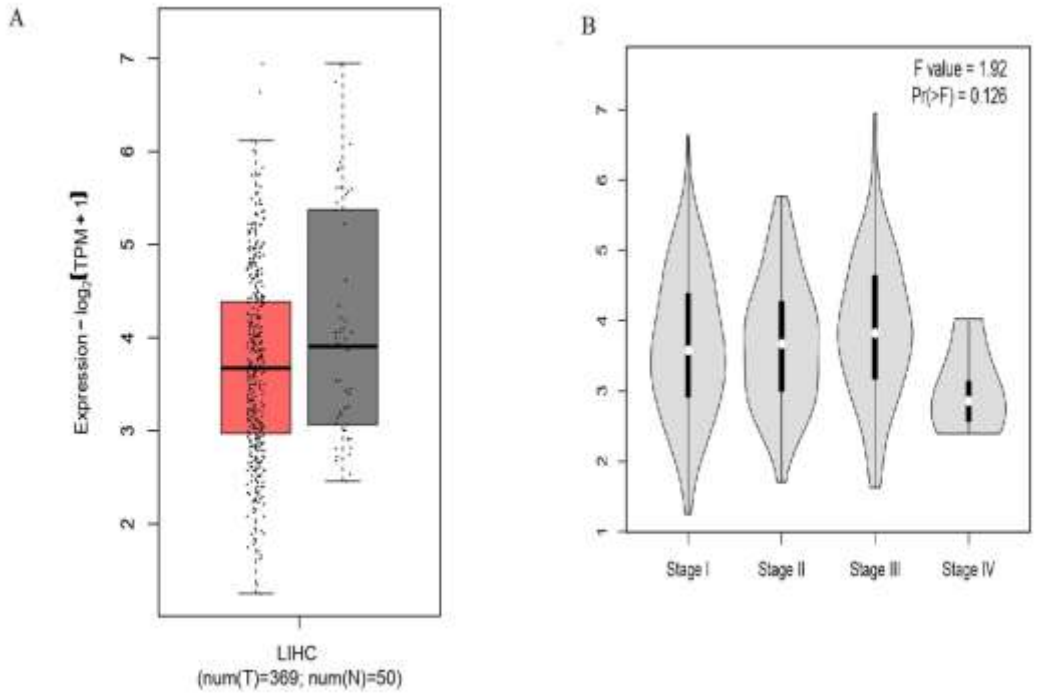


Figure 3: Validation of PIM1 across different stages.

3.4 Promoter methylation of PIM1 in LIHC and normal control samples

Therefore, we analyzed the difference in promoter methylation of PIM1 in LIHC samples compared to normal control samples using the UALCAN database (Figure 4). Our analysis revealed significant variation, particularly hypermethylation, in the promoter methylation level of PIM1 in LIHC compared to normal control samples. This observation suggests potential epigenetic dysregulation of PIM1, highlighting its involvement in LIHC pathogenesis. Such findings contribute to our understanding of the molecular mechanisms underlying LIHC development and provide insights into the role of PIM1 as a potential biomarker or therapeutic target in LIHC management.

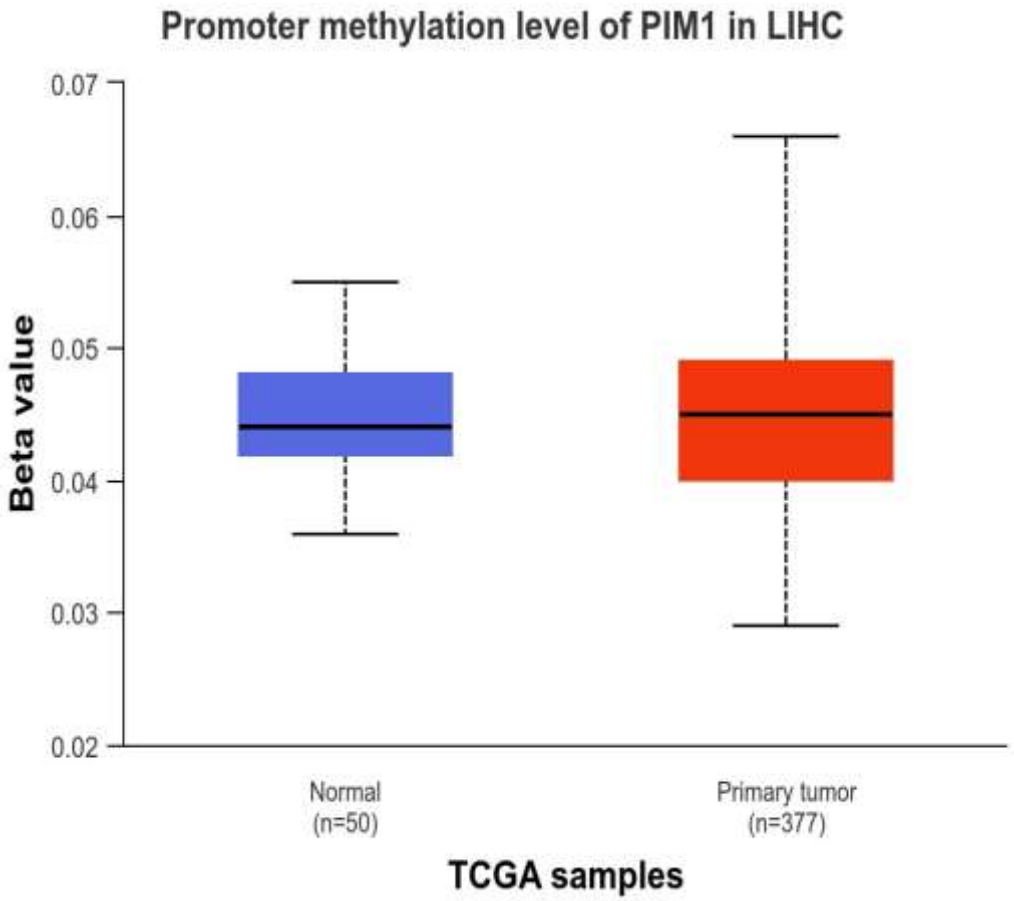


Figure 4: Promoter methylation pattern of PIM1 in LIHC and normal control samples.

3.5 Promoter methylation of PIM1 in LIHC samples divided based on different clinical parameters

We conducted an analysis of different parameters to explore the promoter methylation of PIM1 in LIHC (Figure 5). Initially, we investigated PIM1 promoter methylation across various LIHC stages compared to normal samples. Our findings indicated variations among stages, with stages 1, 2, and 3 displaying hypermethylation, while stage 4 showed hypomethylation (Figure 5A). Next, we examined PIM1 promoter methylation across different racial groups of LIHC patients and observed hypermethylation in PIM1 promoter regions across all racial groups compared to normal control samples (Figure 5B). Subsequently, we analyzed PIM1 promoter methylation according to patient gender, revealing gender-specific variations with both females and males exhibiting hypermethylation (Figure 5C). Finally, we investigated PIM1 promoter methylation with respect to patient age, uncovering varying methylation levels across different age groups (Figure 5D). These comprehensive analyses highlight the complex relationship between PIM1 promoter methylation and various clinical parameters in LIHC, providing insights into the multi-layered mechanisms underlying PIM1 expression regulation in LIHC pathogenesis.

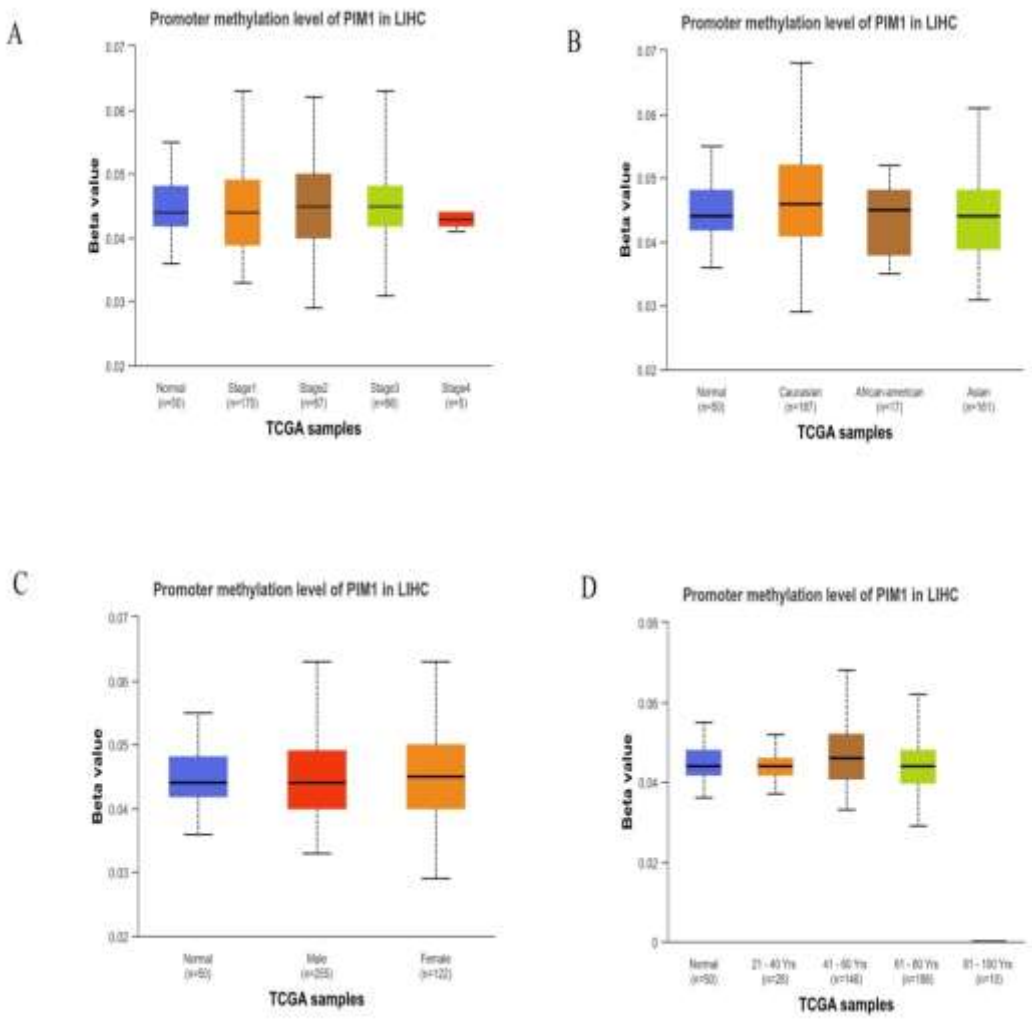


Figure 5: PIM1 promoter methylation pattern across different clinical parameters.

3.6 Survival analysis of PIM1

Utilizing the KM plotter tool, we conducted an analysis to assess the overall survival (OS) and relapse-free survival (RFS) of LIHC patients based on PIM1 gene expression. Our investigation revealed a significant association between PIM1 gene expression levels and patient survival outcomes. Specifically, LIHC patients with low PIM1 expression exhibited markedly higher overall survival rates compared to those with high PIM1 expression (Figure 6A). Furthermore, in the relapse-free survival (RFS) analysis, LIHC patients with high PIM1 expression experienced shorter RFS durations. These findings underscore the pivotal role of PIM1 in influencing the survival outcomes of LIHC patients, highlighting its potential clinical relevance as a prognostic marker in LIHC management.

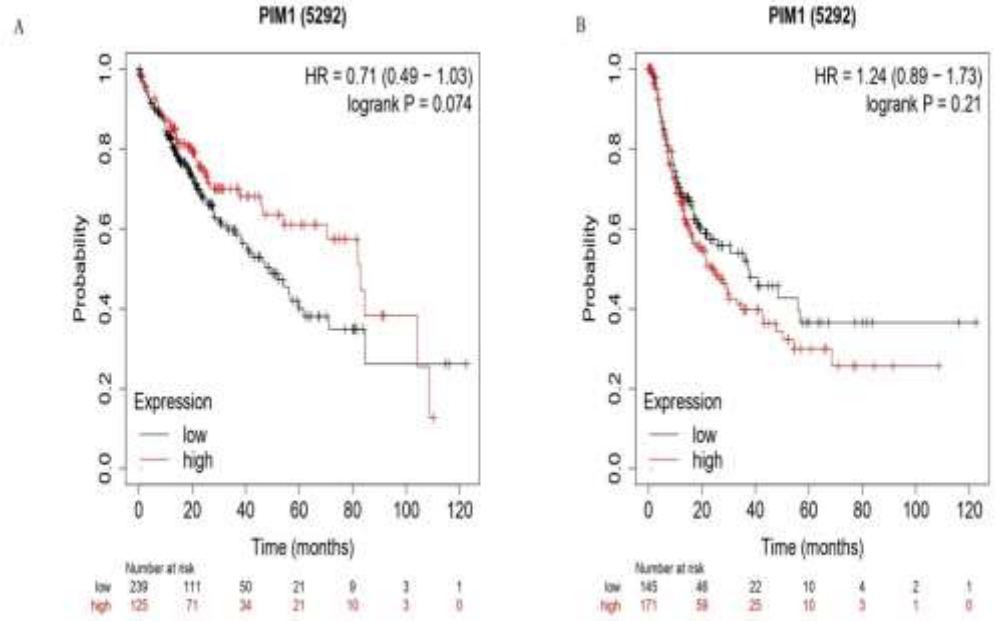
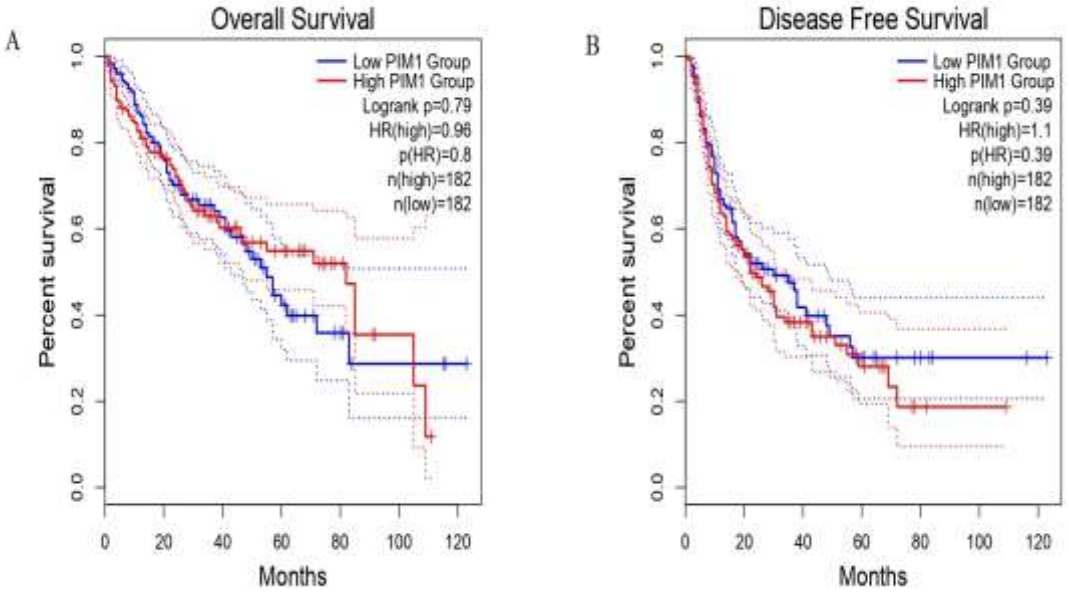


Figure 6: KM survival curve (OS, RFS) of PIM1 in LIHC patients.

3.7: Survival validation of PIM1 on additional LIHC data set

In our study using the GEPIA2.0 database, we investigated the prognostic value of PIM1 expression in LIHC. We divided LIHC patients into low and high expression groups of PIM1. Our findings showed that high PIM1 expression in LIHC was associated with better overall survival (OS) compared to low PIM1 expression (Figure 7A). Additionally, we observed that low PIM1 expression levels were associated with better disease-free survival (DFS) in LIHC compared to the high expression group (Figure 7B). These results suggest that PIM1 expression levels may serve as a prognostic indicator in LIHC, where higher expression correlates with improved OS and lower expression correlates with better DFS.



3.8 Mutational analysis of PIM1 in LIHC

Utilizing the cBioPortal platform, we directed a comprehensive mutational analysis of PIM1 in LIHC. In our study, no significant mutation was observed of PIM1 (Figure 8).

Figure 8: Oncoplot of PIM1 in LIHC samples.

4. Discussion

In this study, we investigated PIM1 expression, prognosis, methylation, survival, and mutation in LIHC using various bioinformatics online tools. We utilized OS and DFS analyses to validate significant differences in hepatocellular carcinoma. Our findings highlight the substantial impact of PIM1 on human biology and suggest a potential association between PIM1 expression and LIHC proliferation, proposing PIM1 as a candidate regulator in LIHC pathogenesis.

In liver hepatocellular carcinoma (LIHC), a significant proportion of non-tumor cells in the microenvironment are tumor-infiltrating immune cells. Tumors exhibiting immune-invasive characteristics tend to have longer survival and lower recurrence rates following resection or transplantation [31]. Approximately 30% of early LIHC cases involve immune-invasive tumors, contrasting with 25% that do not exhibit immune invasion [32]. In the fight against cancer, immunotherapy strategies such as immune checkpoint blockade have emerged as robust therapeutic approaches [33]. Patients with LIHC should be closely monitored for responses to immune checkpoint blockades. Studies suggest that epigenetic modifiers like histone deacetylase inhibitors can enhance antitumor immune responses by increasing immune checkpoint expression during immunotherapy. This highlights the potential of combining epigenetic therapies with immunotherapy to improve outcomes in LIHC treatment.

In general, PIM1 plays a pivotal role in uncontrolled cell growth, survival, and metastasis, and it has been identified as a promising therapeutic target in various malignant tumors. Dysregulation of PIM kinases, including PIM-1, is implicated in the development and progression of pancreatic cancer. PIM-1 is known to regulate cell proliferation, the cell cycle, apoptosis, and chemoresistance across multiple tumor types, including pancreatic cancer [34, 35]. However, the regulatory roles and mechanisms of PIM1 in pancreatic cancer remain unclear. Studies have shown that down-regulation of PIM1 can enhance the chemosensitivity of prostate cancer cells [36]. Elevated levels of PIM1 have been observed not only in cancer tissues but also in the cancer stroma in previous research [37]. The prognostic value of PIM-1 levels in cancer tissues remains controversial. For instance, Peng et al. found that PIM-1 expression levels in colon cancer tissues were not prognostic [38], whereas Liu et al. reported that high PIM-1 expression levels were associated with poor prognosis in patients with esophageal squamous cell carcinoma [39]. These findings underscore the complex and context-dependent roles of PIM1 in different cancer types, highlighting its potential both as a therapeutic target and as a prognostic biomarker.

Conclusion

In our current investigation, we utilized UALCAN datasets to assess PIM1 expression in LIHC. Our analysis revealed down-regulated PIM1 expression across various stages, types, ages, genders, and racial groups in LIHC. Regarding tumor development, our study demonstrated significantly lower PIM1 expression levels in LIHC tissues compared to normal tissues. Additionally, using the KM plotter tool, we analyzed the impact of PIM1 expression on overall survival (OS) and disease-free survival (DFS) in LIHC patients. Our findings indicated that LIHC patients with high PIM1 expression experienced significantly worse OS and shorter DFS compared to those with low PIM1 expression levels. Moreover, our study identified PIM1 expression level in tissue as an independent poor prognostic factor. Further investigations are warranted to fully elucidate the prognostic value and mechanistic roles of PIM1 expression in various cancers, including LIHC.

Conflict of interest

None

Acknowledgement

None

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